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VENTILATORY ACCLIMATIZATION IN WOMEN TO HIGH ALTITUDE

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Stephen R. Muza, Paul B. Rock, Charles S. Fulco, Stacy Zumudio, Barry Braun, John T. Reeves, Allen Cymerman, Gail E. Butterfield and Lorna G. Moore

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The purpose of this study was to test the hypotheses that women ascending to high altitude in their early luteal phase will have higher resting ventilations and accelerated ventilatory acclimatization compared to women in their follicular phase. Furthermore, given the proportionally greater ventilation in women compared to men, we postulated that women will have higher resting ventilations and accelerated ventilatory acclimatization compared to men at the same altitude. Studies were conducted on 22 nonsmoking, eumenorrheic sea level residents of average fitness (mean±SD age of 22.5 ± 3.7 yr; weight of 65.6 ± 11.2 kg; and height of 166.1 ± 5.5 cm). All had corresponding ovarian steroid hormone profiles and menstrual cycle histories which substantiated their normal menstrual cycle status. The resting ventilation and ventilatory chemosensitivities (HVR and HCVR) in 14 of these women were measured during their follicular phase and in 7 women in the luteal phase of their menstrual cycle at sea level and again at 4,300 m altitude for 12 days. Resting ventilation (VE or expressed as PETCO2) was similar in the follicular and luteal phase women at sea level and during the first 3 days at high altitude. Furthermore, the rate of decline in PETCO2 during the first 3 days at high altitude relative to sea level was identical (0.15 ± 0.08 mmHg PETCO2/h) between the follicular and luteal groups respectively. Likewise, the slopes of the isocapnic HVR, and HCVR and x-intercept of the HCVR, were not significantly different between the follicular and luteal groups at sea level and high altitude. The women's data was pooled and compared to previously published data on 37 men at the same elevation. As expected, women had higher resting ventilation at sea level compared to the men. However, at high altitude the women's resting ventilations were nearly identical to the men's. We conclude that menstrual cycle phase does not have a meaningful effect on ventilatory acclimatization at 4,300 m and that women have similar levels of ventilation and follow a similar time course for ventilatory acclimatization to that previously reported for men at 4,300 m elevation.

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Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of volunteers in research.

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USARIEM TECHNICAL REPORT 99-8

VENTILATORY ACCLIMATIZATION IN WOMEN TO HIGH ALTITUDE

Prepared by

Stephen R. Muza, Paul B. Rock, Charles S. Fulco, Stacy Zumudio, Barry Braun, John T. Reeves, Allen Cymerman, Gail E. Butterfield and Lorna G. Moore

U.S. ARMY RESEARCH INSTITUTE
OF
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BACKGROUND

Women currently comprise approximately 15% of active duty military personnel and 22% of the Reserve and Guard personnel in the U.S. Army. Yet, while mountainous environments are likely areas of conflict, there is little information available on women's responses to high terrestrial elevations, especially as they relate to hormonal changes associated with the menstrual cycle. Thus, many aspects of altitude acclimatization in women and the impact it may have on military operations remain poorly defined.

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EXECUTIVE SUMMARY

Humans compensate for the decreased partial pressure of oxygen (PIO_2) of high altitude by progressively increasing ventilation. However, almost all of what we know about ventilatory acclimatization to high altitude is based on studies of males. In eumenorrheic females, resting ventilation at low altitude increases in the luteal phase of the menstrual cycle. On the other hand, there are no reports of menstrual cycle phase effects on ventilation at high altitudes. Therefore, given the effects of the menstrual cycle on resting ventilation at low altitudes, we postulated that women ascending to high altitude in their early luteal phase will have higher resting ventilations and accelerated ventilatory acclimatization compared to women in their follicular phase. Furthermore, given the proportionally greater ventilation in women compared to men, we postulated that women will have higher resting ventilations and accelerated ventilatory acclimatization compared to men at the same altitude. To characterize the magnitude and time course of ventilatory acclimatization to 4300 m elevation, we measured resting ventilation, hypoxic ventilatory responsiveness (HVR) and hypercapnic ventilatory responsiveness (HCVR) in 22 nonsmoking, eumenorrheic sea level residents. Studies were completed in 14 of these women during their follicular phase and in 7 women in the luteal phase of their menstrual cycle at sea level and again at 4,300 m altitude for 12 days. Resting ventilation ($\dot{V}E$ or expressed as $P_{ET}CO_2$) was similar in the follicular and luteal phase women at sea level and during the first 3 days at high altitude. Furthermore, the rate of decline in $P_{ET}CO_2$ during the first 3 days at high altitude relative to sea level was identical between the follicular and luteal groups, respectively. Likewise, the slopes of the isocapnic HVR, and HCVR and x-intercept of the HCVR, were not significantly different between the follicular and luteal groups at sea level and high altitude. The women's data were pooled and compared to previously published data on 37 men at the same elevation. On the basis of this comparison, we conclude that women rapidly ascending to 4,300 m have similar levels of ventilation and follow a time course for ventilatory acclimatization similar to that previously reported for men under similar ascent conditions.

INTRODUCTION

Human acclimatization to high altitude has received a great amount of scientific inquiry over the last 100 years. Humans compensate for the decreased PIO_2 by progressively increasing ventilation during sojourns to high altitude (3). Following rapid ascent to 4,300 m elevation, ventilation increases during the first 6-8 days (22). The rise in ventilation produces a decrease in PaCO2 and increases in hypoxic and hypercapnic ventilatory chemosensitivity (33). Relative to the number of studies of men, few studies have specifically examined ventilatory adaptations in women to high altitude. A common finding of these studies of women (6,13,16) is that women have a greater hyperventilation at altitude than men. This has led to the speculation that the ventilatory stimuli from the ovarian hormones, progesterone and estradiol, may be augmenting the hypoxic stimulation of ventilation at high altitude. However, no studies have examined the possible role of ovarian hormones on ventilation at high altitude.

Progesterone appears to be the ovarian hormone primarily responsible for increasing ventilation in the luteal phase, although estradiol potentiates the ventilatory effects of progesterone (1,23,24). The ovarian hormones increase ventilation by acting on receptor-mediated mechanisms at both central and peripheral sites (2,5,15,23,31). In normally menstruating women at low altitudes, resting ventilation is elevated in the mid-luteal phase compared to the follicular phase (9-12,17,18,24,26,28-30,32). The most consistent finding of these studies is a lowering of $PACO_2$ or $PaCO_2$ in the luteal vs. follicular phase. Similarly, ventilation is substantially increased during pregnancy when endogenous progesterone levels can rise nearly 10-fold greater than typically seen in the luteal phase (7). Other studies have reported increased ventilation in response to exogenous administration of progestins (medroxyprogesterone acetate) in both women and men (14,24,27).

Menstrual cycle phase effects on hypoxic and hypercapnic ventilatory chemosensitivity vary more than on resting ventilation. In normally menstruating women, ventilatory chemosensitivity was found elevated in many of these studies (9-11,17,26,28,32), but was also reported unchanged in a nearly equal number of studies (9,24,29,30,32). The lack of a consistent and strong correlation between hypoxic and hypercapnic ventilatory responsiveness and plasma progesterone may be

affected by the rather large inherent variability in these measures of ventilatory drive (25).

No studies have examined the possible effects of menstrual cycle phase on ventilatory acclimatization to high altitude. Therefore, the first purpose of this study was to test the hypotheses that women ascending to high altitude in their early luteal phase will have higher resting ventilations and accelerated ventilatory acclimatization compared to women in their follicular phase. Secondly, given the proportionally greater ventilation in altitude acclimatized women compared to acclimatized men, we postulated that women will have higher resting ventilations and accelerated ventilatory acclimatization compared to men at the same altitude.

METHODS

SUBJECTS

Twenty-seven women participated in this study. All subjects gave written informed consent prior to their participation. The subjects were nonsmoking, eumenorrheic sea level residents of average fitness. No subject had altitude exposure greater than 1,500 m within the 6 months prior to the study. Twenty-two subjects completed the ventilatory protocols at sea level and high altitude, and had corresponding ovarian steroid hormone profiles and menstrual cycle histories, which substantiated their normal menstrual cycle status. These 22 women had a mean (±SD) age of 22.5 ± 3.7 yr; weight of 65.6 ± 11.2 kg; and height of 166.1 ± 5.5 cm.

STUDY DESIGN

This study used a repeated measures design in which the resting ventilation and ventilatory chemosensitivity of women lowlanders were measured during either their follicular or luteal phase of their menstrual cycle at sea level and again at 4,300 m altitude. Due to logistical constraints, the study was conducted during the spring and summer of 1996 and 1998. In 1996, attempts were made to study 19 subjects at sea level in both their follicular and luteal phases. Thus, sea level experiments were conducted during two identical 12-day test periods separated by 1 to 8 weeks, depending upon personal schedule requirements. Subjects were then divided into two groups, with half assigned to arrive at high altitude at the beginning of their follicular

phase and the other group to arrive at the beginning of their luteal phase (see menstrual cycle documentation). In 1998, 8 subjects were studied during a single 12-day test period at sea level. Also, because of difficulties in scheduling tests to coincide with the onset of the follicular and luteal phases, subjects entered testing without specific regard to the status of their menstrual cycle phase. After sea level testing was completed, analysis of serum progesterone and estradiol concentrations was used to identify the menstrual cycle phase in which testing was performed. Attempts were then made to schedule subjects to commence their high altitude test phase in the same menstrual cycle phase in which they completed their sea level testing. The 12-day test periods in 1996 and 1998 were nearly identical. The primary difference between the 2 years was the scheduling of exercise tests, which did not impact the resting ventilatory studies.

All sea level studies were conducted at facilities of the Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, USA (elevation 25 m). Approximately 1-3 months after completing the sea level studies, subjects were transported by airline to Colorado Springs, CO, and within a few hours by car to the 4,300 m summit of Pikes Peak where 12 days of studies were conducted within the U.S. Army Pikes Peak Laboratory Facility. The subject's day of arrival on the summit was designated day 1 of the high altitude study period. During the sea level and altitude test phases, subjects were maintained on a caffeine-free, controlled diet designed to maintain body weight and minimize the influence of changes in substrate availability. Subjects kept an activity log and strived to maintain a regular daily program of light-to-moderate intensity exercise during both sea level and altitude test phases.

MENSTRUAL CYCLE DOCUMENTATION

Each subject kept a menstrual cycle diary noting the dates of her menses, the duration of her menstrual cycle and the day of detection of luteinizing hormone in her urine (LH: OvuQuick ovulation prediction kit, Becton-Dickson, Rutherford, NJ). A minimum of a 3-month menstrual cycle history was documented by diary or by information provided by the subject prior to starting studies. The follicular phase was defined as beginning with the first day of menses and lasting until detection of LH at which time the luteal phase began. In 1996, subjects began their studies the day after their menses began or urine LH was detected. In 1996, blood samples for analysis of ovarian steroid hormones was obtained by venipuncture at sea level on days 3, 10 and

12 and at high altitude on days 3, 8, 10 and 12. In 1998, ovarian steroid hormones were assayed at sea level and high altitude on days 1, 3, 6, 9, 10, and 12. After all testing was completed, serum concentrations of progesterone and estradiol were determined by RIA (Diagnostic Products Corp. Coat-A-Count Kit) and/or chemiluminescent enzyme immunoassay (Diagnostic Products Corp. Immulite Kits) and used to finalize menstrual cycle phase assignments in conjunction with each subject's menstrual cycle diary.

RESTING VENTILATION AND VENTILATORY CONTROL TESTS

At sea level, resting ventilation, isocapnic hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) were measured on days 1 or 2 and 7 or 8 of each sea level 12-day test period. Sea level ventilatory studies were usually, but not always, performed in the morning. At high altitude, resting ventilation studies were performed the afternoon of the 1st day (2-3 h after arrival) and on the mornings of days 2, 3, 5, 7 and 12 on the summit. Ventilatory chemosensitivity studies (HVR, HCVR) were conducted on the mornings of days 2, 7 and 12. At both sea level and high altitude, ventilatory studies were performed more than 2 hours after a meal.

All ventilatory tests were performed with the volunteers resting in a seated position. The volunteer breathed through a low resistance respiratory valve and breathing circuit connected to a computer-controlled, breath-by-breath metabolic measurement system (Vmax229, SensorMedics Corp, Yorba Linda, CA). Resting ventilation tests measured breath-by-breath: minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide elimination ($\dot{V}CO_2$), and end tidal oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$). Simultaneously, blood oxygen saturation (SpO_2) was measured by pulse oximetry and heart rate (HR) by 3-lead ECG (Nellcor N-200). The resting ventilation tests were about 20 minutes in duration. Resting ventilatory parameters were obtained and the mean values calculated from the last 8-10 minutes of the session.

The HVR was measured using a progressive isocapnic hypoxia protocol of 7 to 10 minute duration. Subjects accommodated to the breathing circuit on room air for 5 minutes prior to beginning the HVR test. At sea level the test began with the subject breathing room air, where as at high altitude the test was initiated with several minutes of breathing an FIO_2 of 0.36 to restore PAO_2 to sea level values. In 1996, the PIO_2 was

slowly reduced by addition of nitrogen to the circuit; and isocapnia was maintained by adding CO_2 to the inspired gas. The target $P_{ET}CO_2$ for isocapnia was either that measured during the baseline period on room air at sea level, or the $P_{ET}CO_2$ during the last minute of the hyperoxia baseline period at high altitude. In 1998, the progressive hypoxia was achieved by rebreathing from a spirometer with an initial volume of gas (described above) equal to the subject's FVC+1 L. With this rebreathing method, isocapnia was maintained by selectively scrubbing CO_2 with barium hydroxide from the rebreathing circuit. These changes simplified the HVR protocol and did not alter the circuit's air flow resistance or dead space volume. Otherwise, the 1998 HVR protocol was identical to 1996. Two HVR tests separated by at least 10 minutes were performed. If the two HVR measurements disagreed by greater than 30%, a third HVR test was performed. All ventilatory parameters were averaged over 10 breaths. The HVR is reported as the slope (HVRs: $\Delta\dot{V}E/\Delta SpO_2$, $l \bullet min^{-1} \bullet \%^{-1}$) calculated using least squares regression. For each subject the reported HVR is the average of the two HVR tests in closest agreement.

The HCVR was performed using the same equipment described above, configured as a rebreathing system, using the protocol as described by Read et al. (21). The volunteer breathed room air during the baseline period. After a stable $P_{ET}CO_2$ was attained, she rebreathed a gas mixture with an initial composition of 7% CO_2, balance O_2 for 4-5 minutes. One HCVR was performed during each test session. All ventilatory parameters were averaged over 10 breaths. The slope (HCVRs: $\Delta\dot{V}E/\Delta PCO_2$, $l \bullet min^{-1} \bullet mmHg^{-1}$) was calculated using least squares regression. The extrapolated x-axis intercept (HCVRx) is reported as the PCO_2 (mmHg).

ARTERIAL BLOOD GASES

In the first year of this study, resting arterial samples were drawn anaerobically from an indwelling radial artery catheter on day 10 at sea level and high altitude. The samples were immediately placed on ice and analyzed within 30 min for PaO_2, $PaCO_2$, and pHa (ABL 300, Radiometer, Copenhagen, Denmark).

STATISTICAL ANALYSIS

Differences between menstrual cycle phases were compared by a two-factor ANOVA (menstrual cycle phase and time at altitude) with repeated measures in one factor (time at altitude). Tukey post hoc comparisons were used to identify significant

differences among means. Differences between menstrual cycle phases within a subject at sea level were compared with a Paired T-test. Tests of possible relationships between each subject's resting ventilatory parameters and ovarian hormone concentrations were performed using the Pearson Product-Moment Correlation method. All statistical analyses were performed using Sigma Stat v2.03 (SPSS, Inc.). Values are given as means±SD. Significant differences are presented with its 95% Confidence Interval (CI).

RESULTS

MENSTRUAL CYCLE PHASE EFFECTS

Post-study analysis of plasma progesterone and estradiol, along with menstrual cycle histories, revealed that 7 women were in their luteal phase and 14 were in their follicular phase upon arrival at 4,300 m. Each of these subjects had sea level studies in the corresponding cycle phase. However, over the course of 12 days of studies, many of the women transitioned from one cycle phase to the other, complicating the analysis of menstrual cycle phase effects. This was particularly apparent at high altitude where 8 women transitioned during the 12 day sojourn. Therefore, analysis was limited to the first 3 days at high altitude and the corresponding menstrual cycle phase tests at sea level in order to have a clear distinction between the menstrual cycle phases and its possible effects on ventilatory acclimatization to altitude.

The resting serum progesterone and estradiol concentrations (Table 1) were higher at sea level (+6.5 $ng \cdot ml^{-1}$, p=0.001, 95%CI= 4.3 to 8.6 $ng \cdot ml^{-1}$ progesterone and +41.8 $pg \cdot ml^{-1}$, p=0.007, 95%CI=13.1 to 70.4 $pg \cdot ml^{-1}$ estradiol) and day 3 at high altitude (+5.3 $ng \cdot ml^{-1}$, p=0.003, 95%CI=2.0 to 8.6 $ng \cdot ml^{-1}$ progesterone and +48.2 $pg \cdot ml^{-1}$, p=0.002, 95%CI=19.9 to 76.6 $pg \cdot ml^{-1}$ estradiol) in the luteal phase women compared to the follicular phase women. As shown in Table 1, resting ventilation ($\dot{V}_E$ or expressed as $P_{ET}CO_2$) was similar in the follicular and luteal phase women at sea level and during the first 3 days at high altitude. Furthermore, the rate of decline in $P_{ET}CO_2$ during the first 3 days at high altitude relative to sea level was identical (0.15 ± 0.08 mmHg $P_{ET}CO_2 \cdot h^{-1}$) between the follicular and luteal groups, respectively. Likewise, HVRs, HCVRs and HCVRx, were not significantly different between the follicular and luteal groups at sea level and high altitude (Table 1). The only pulmonary variable that was

significantly different between the two groups was the resting $PaCO_2$ at sea level. In the 5 luteal phase subjects the $PaCO_2$ was lower (-2.4 mmHg, p=0.032, 95%CI=-5.0 to 0.2 mmHg) compared to 9 follicular phase subjects on day 10 at sea level (38.8 ± 2.4 vs. 41.2 ± 2.0 mmHg, respectively). However, $PaCO_2$ was not measured in the first 3 days at high altitude.

Eleven subjects had sea level studies performed in both their follicular and luteal phases. As shown in Table 2, within subject repeated measures (paired T-test) found lower $P_{ET}CO_2$ (-2.3 mmHg, p=0.005, 95%CI -3.8 to -0.7 mmHg) in the luteal phase compared to their follicular phase measurements. Arterial PCO_2, measured on 9 of these subjects 1-2 days after the ventilatory measures, was also lower (-1.8 mmHg, p=0.027, 95%CI -3.6 to 0.1 mmHg) in the luteal phase compared to the follicular phase. Although HVRs and HCVRs were not different between the follicular and luteal phases in these 11 women, the HCVRx was lower (-2.1 mmHg, p=0.02, 95%CI -4.1 to -0.1 mmHg) in the luteal compared to follicular phase.

OVARIAN HORMONE EFFECTS

Given that ovarian hormone concentrations are not stable during either the follicular or luteal phases, we evaluated the effects of the daily fluctuations in progesterone and estradiol on ventilatory acclimatization. Illustrated in Figures 1-4 are the relationships between the ovarian hormones and resting ventilation ($P_{ET}CO_2$), HVRs, HCVRs, and HCVRx. These plots clearly illustrate the considerable variability between subjects in both the resting ventilation data and ovarian hormone concentrations and the effects of ventilatory acclimatization previously noted. However, there were no statistically significant correlations observed between any of these resting ventilatory parameters and the subjects ovarian hormone concentrations at sea level or any day at altitude.

VENTILATORY RESPONSES INDEPENDENT OF OVARIAN HORMONE STATUS

Given no significant differences between follicular and luteal groups at high altitude, the data were pooled. Within a few hours of arrival at 4,300 m, resting $P_{ET}CO_2$ was significantly lower and $\dot{V}_E$ was greater than at sea level (Table 3). As expressed by the decreasing $P_{ET}CO_2$, ventilation continued to increase ($p<0.001$) throughout the 12 days of high altitude residence, although the change between days 7 and 12 was not statistically significant. Arterial oxygen saturation increased ($p<0.05$) rapidly during

the first 5 days, with no significant improvement thereafter. On day 10, resting $PaCO_2$, pHa, and PaO_2 (28.9 ± 2.1, 7.446 ± 0.017, 51.0 ± 3.5 mmHg, n=12) were significantly ($p<0.001$) different compared to sea level day 9 (40.4 ± 2.4 mmHg, 7.415 ± 0.020, 107.4 ± 10.1 mmHg, n=14), respectively. The HVRs and HCVRs were not increased on day 2, but were higher ($p<0.05$) by day 7 with no further increase noted on day 12 (Table 3). However, the HCVRx did show a decrease ($p<0.05$) from sea level values on day 2, with progressive decreases to day 12.

There was a wide distribution in $P_{ET}CO_2$ at both sea level and high altitude, which ranged from 34.3 to 42.2 mmHg at sea level with a similar spread of 10 mmHg between the minimum and maximum $P_{ET}CO_2$ at all days at high altitude (Fig. 5). The $P_{ET}CO_2$ measured on all days at high altitude was positively correlated with the preascent normoxic $P_{ET}CO_2$ at sea level (Table 4).

Table 1. Resting ventilatory measures at 4300 m in the follicular and luteal phases of the menstrual cycle.

	FOLLICULAR				LUTEAL			
	SL	Day 1	Day 2	Day 3	SL	Day 1	Day 2	Day 3
N	14	14	14	12	7	7	6	6
Progesterone ($ng \cdot ml^{-1}$)	0.9 ± 0.8			0.9 ± 0.5	7.4 ± 3.8			5.3 ± 5.9
Estradiol ($pg \cdot ml^{-1}$)	46 ± 27			52 ± 28	87 ± 31			102 ± 37
$\dot{V}E$ ($l \cdot min^{-1}$)	7.7 ± 2.4	9.2 ± 1.4	10.2 ± 1.3	10.0 ± 1.9	8.0 ± 1.1	9.0 ± 2.3	8.6 ± 1.1	9.0 ± 1.1
$P_{ET}CO_2$ (mmHg)	38.1 ± 2.6	35.0 ± 2.0	33.4 ± 2.8	31.5 ± 3.4	38.5 ± 2.1	34.6 ± 3.6	34.2 ± 1.9	32.1 ± 1.3
SpO_2 (%)	98 ± 1	81 ± 4	83 ± 5	83 ± 6	98 ± 1	79 ± 5	80 ± 3	81 ± 5
HVR ($\Delta\dot{V}E/\Delta SpO_2$)	0.58 ± 0.41		0.46 ± 0.28		0.43 ± 0.26		0.39 ± 0.31	
HCVRs ($\Delta\dot{V}E/\Delta PCO_2$)	1.96 ± 0.81		2.29 ± 0.93		1.85 ± 0.61		2.22 ± 0.78	
HCVRx (mmHg)	40.1 ± 4.1		36.8 ± 4.6		39.7 ± 5.5		38.2 ± 1.9	

$\bar{x}$ ± S.D.

Table 2. Menstrual cycle phase effects on resting ventilation at sea level with repeated measures.

	$\dot{V}E$ ($l \cdot min^{-1}$)	$P_{ET}CO_2$ (mmHg)	$PaCO_2$ (mmHg)	HVRs ($\Delta\dot{V}E/\Delta SpO_2$) ($l \cdot min^{-1} \cdot \%^{-1}$)	HCVRs ($\Delta\dot{V}E/\Delta PCO_2$) ($l \cdot min^{-1} \cdot mmHg^{-1}$)	HCVRx (mmHg PCO_2)
Follicular	8.1 ± 2.7	39.3 ± 3.1	40.9 ± 2.2	0.78 ± 0.46	2.28 ± 0.89	40.5 ± 3.3
Luteal	9.2 ± 2.1	37.0 ± 2.4†	39.2 ± 1.6*	0.70 ± 0.38	2.30 ± 0.89	38.5 ± 4.7*

$\bar{x}$ ± S.D., repeated measures in 11 subjects. $PaCO_2$ (n=9) measured 1-2 days after resting ventilatory measures.

† $P < 0.01$, * $P < 0.03$, one tail by paired T-test.

Table 3. Resting ventilatory responses to 4,300 m altitude sojourn. Subjects in follicular and luteal phases grouped together.

	N		$\dot{V}E$ ($l \cdot min^{-1}$)	$P_{ET}CO_2$ (mmHg)	SpO_2 (%)	HVRs ($\Delta\dot{V}E/\Delta SpO_2$) ($l \cdot min^{-1} \cdot \%^{-1}$)	HCVRs ($\Delta\dot{V}E/\Delta PCO_2$) ($l \cdot min^{-1} \cdot mmHg^{-1}$)	HCVRx (mmHg PCO_2)
	F	L						
SL	15	7	8.1 ± 2.0	38.5 ± 2.5	98 ± 1	0.56 ± 0.33	1.91 ± 0.76	39.8 ± 3.3
Day 1*	14	7	9.1 ± 1.7†	34.8 ± 2.5†	80 ± 4†			
Day 2	14	7	9.8 ± 1.4	33.6 ± 2.5†	82 ± 5†	0.44 ± 0.29†	2.05 ± 0.93	36.5 ± 5.4†
Day 3	12	7	9.7 ± 1.7	31.7 ± 2.8†	82 ± 5†			
Day 5	13	7	11.1 ± 1.6	30.6 ± 2.9	86 ± 4			
Day 7	13	9	11.0 ± 1.6	29.7 ± 2.4	86 ± 2	1.19 ± 0.67	2.90 ± 1.48	34.0 ± 3.3
Day 12	16	6	10.9 ± 2.5	28.0 ± 2.3	88 ± 2	1.46 ± 0.93	2.80 ± 1.42	31.6 ± 2.6

F: follicular, L: luteal, $\bar{x}$ ± S.D. * Day 1 measurements made 2-3 h after arrival between 1400 -1600 h.

† indicates significant difference between that high altitude day and Day 12.

Table 4. Relationship (y = ax + b) of preascent normoxic $P_{ET}CO_2$ with high altitude (4,300 m) $P_{ET}CO_2$ values.

Day	a	b	r	n	*P*
1	0.46	17	0.46	21	0.034
2	0.66	8	0.66	21	0.001
3	0.60	9	0.56	19	0.012
5	0.68	4	0.61	20	0.004
7	0.52	10	0.53	22	0.012
12	0.54	7	0.59	22	0.004

Sea level resting $P_{ET}CO_2$ was measured in same menstrual cycle phase as subject's ascent phase.

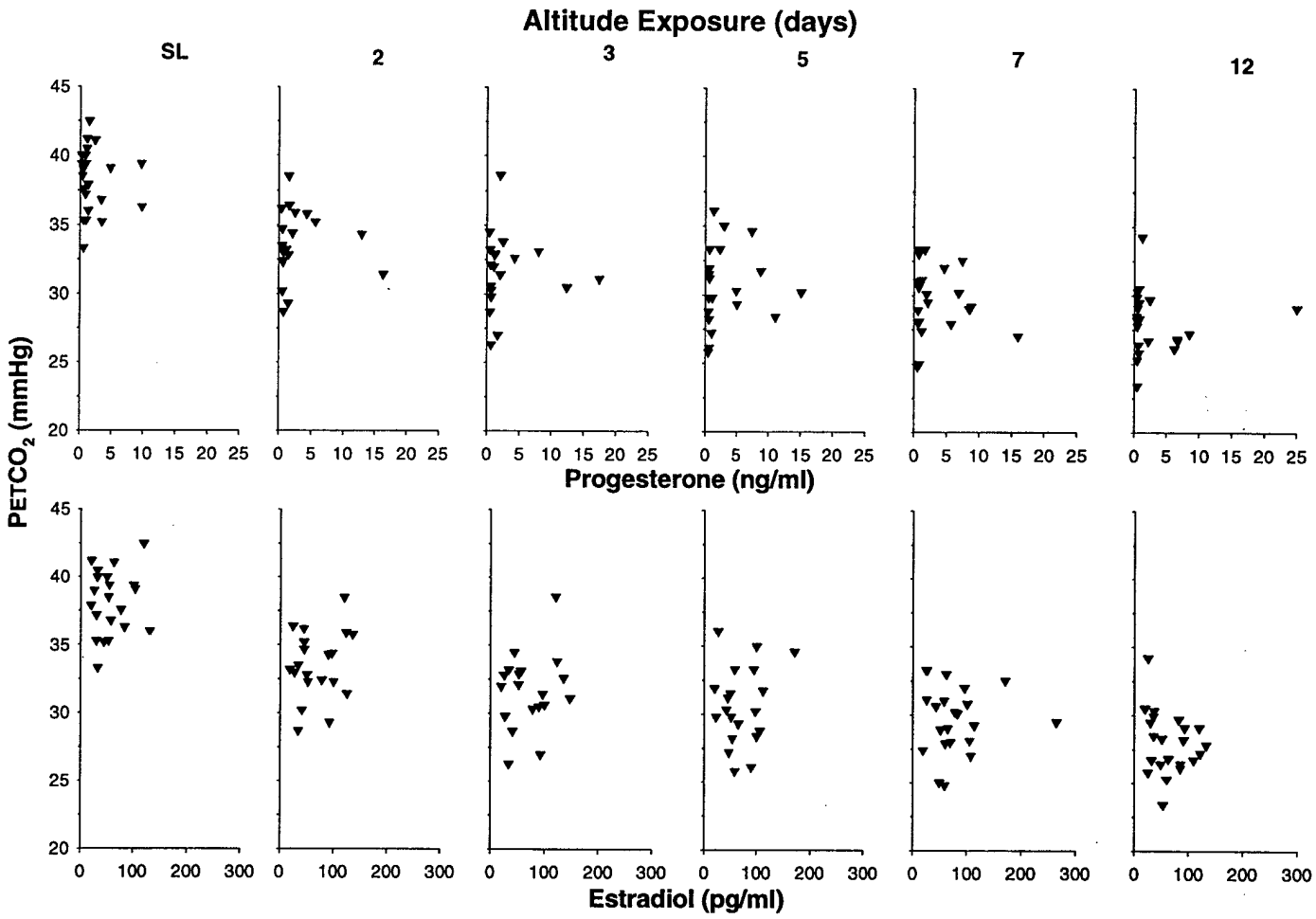

Fig.1. Plots of resting $P_{ET}CO_2$ as a function of each subject's corresponding progesterone and estradiol serum concentrations at sea level and during 12 days sojourn at 4,300 m. On days when serum progesterone and estradiol concentrations were not sampled, values were interpolated using adjacent day values.

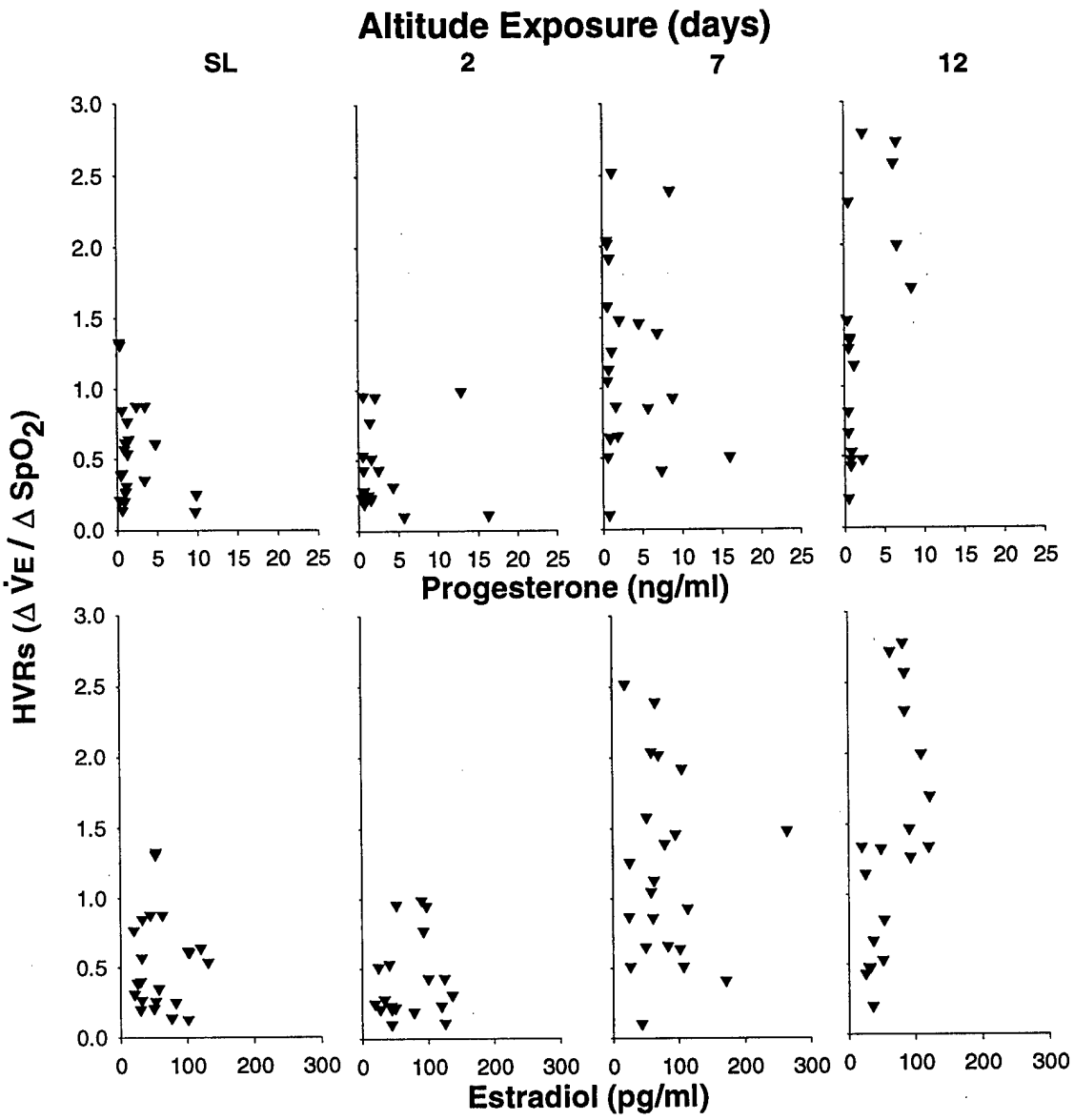

Fig. 2. Plots of resting isocapnic HVR ($\Delta \dot{V}E/\Delta SpO_2$) as a function of each subject's corresponding progesterone and estradiol serum concentrations at sea level and during 12 days sojourn at 4,300 m. Refer to Fig. 1 for further explanation.

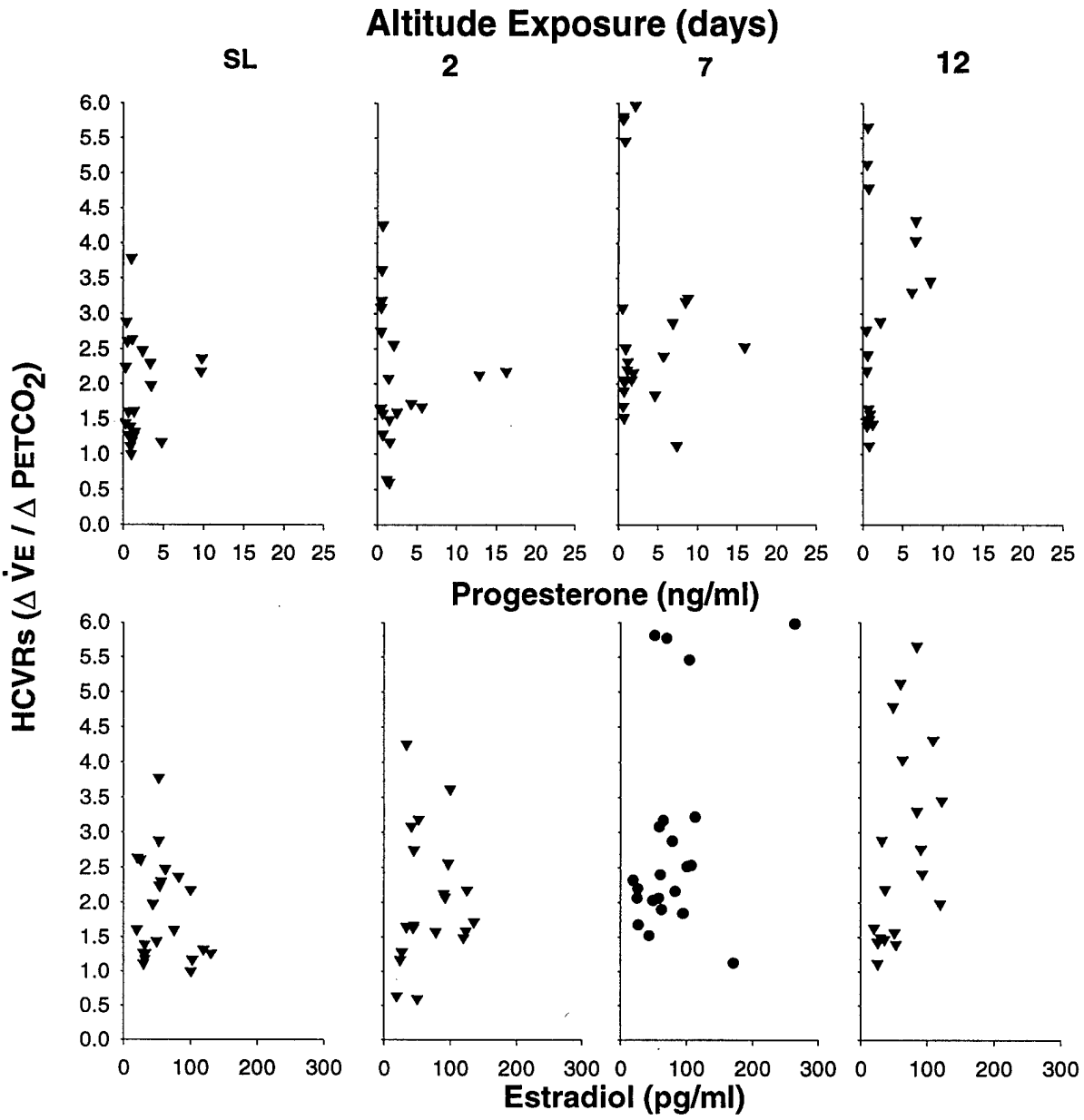

Fig. 3. Plots of resting HCVRs ($\Delta \dot{V}E/\Delta PCO_2$) as a function of each subject's corresponding progesterone and estradiol serum concentrations at sea level and during 12 days sojourn at 4,300 m. Refer to Fig. 1 for further explanation.

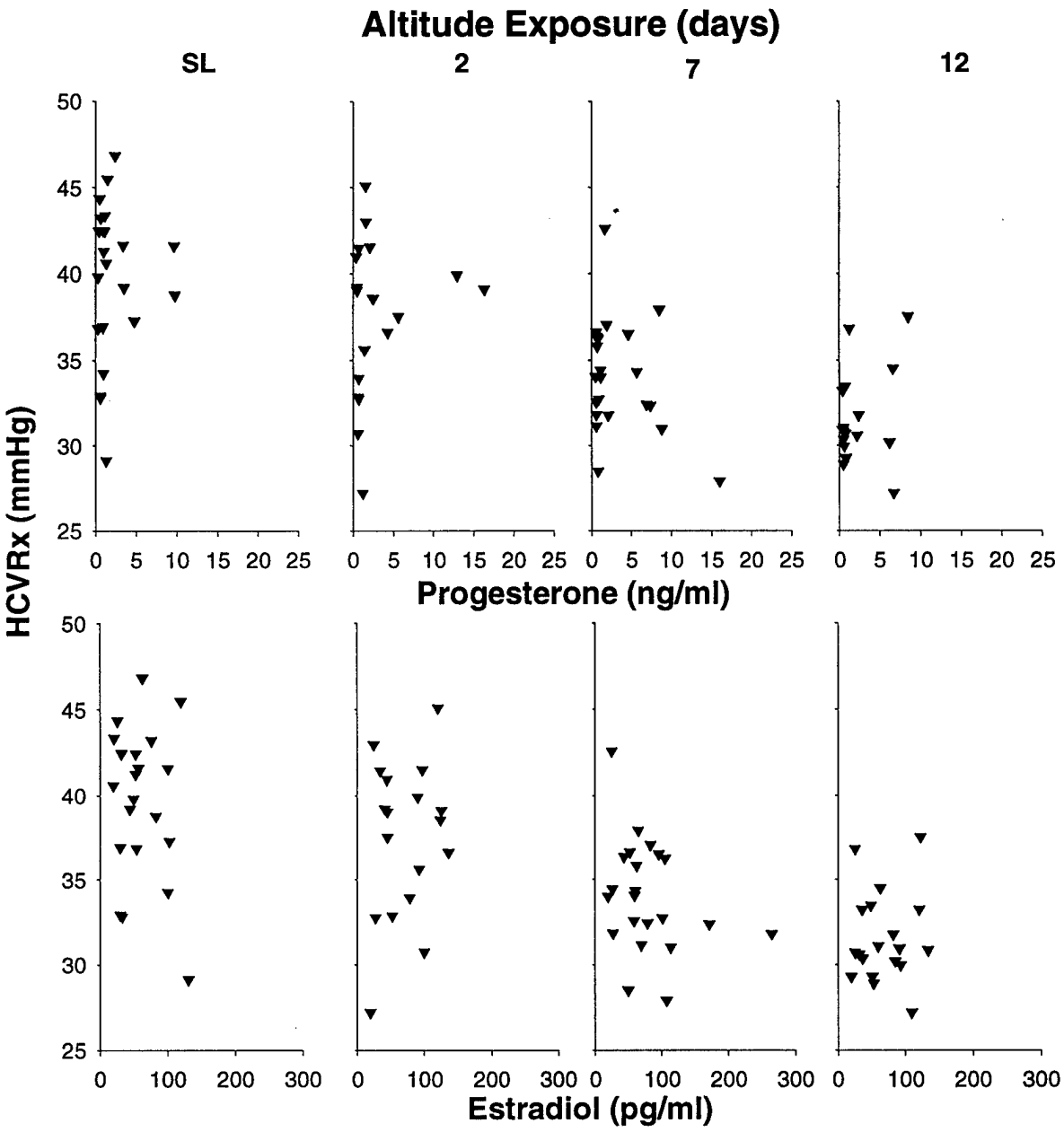

Fig. 4. Plots of resting HCVRx (x-intercept) as a function of each subject's corresponding progesterone and estradiol serum concentrations at sea level and during 12 days sojourn at 4,300 m. Refer to Fig. 1 for further explanation.

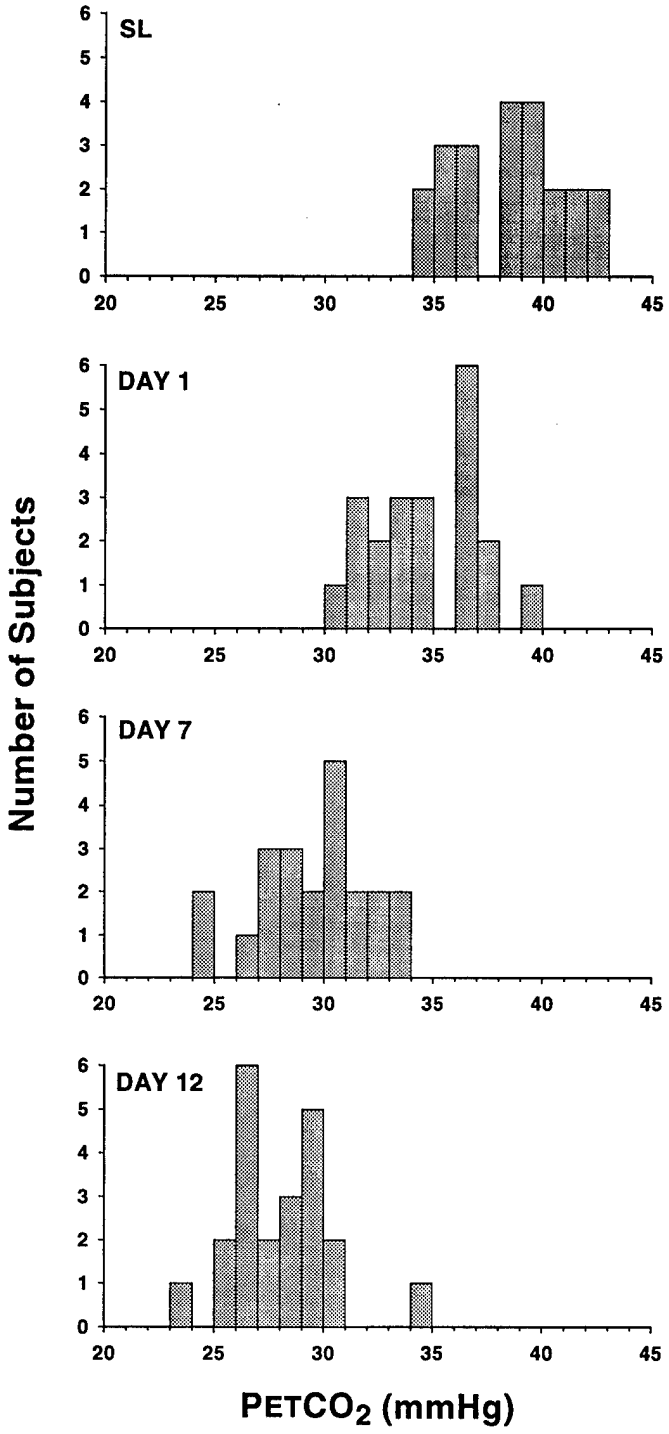

Fig. 5. Histograms showing distribution of $P_{ET}CO_2$ (mmHg) for 22 women subjects at sea level, and on days 1, 7 and 12 on Pikes Peak (4,300 m).

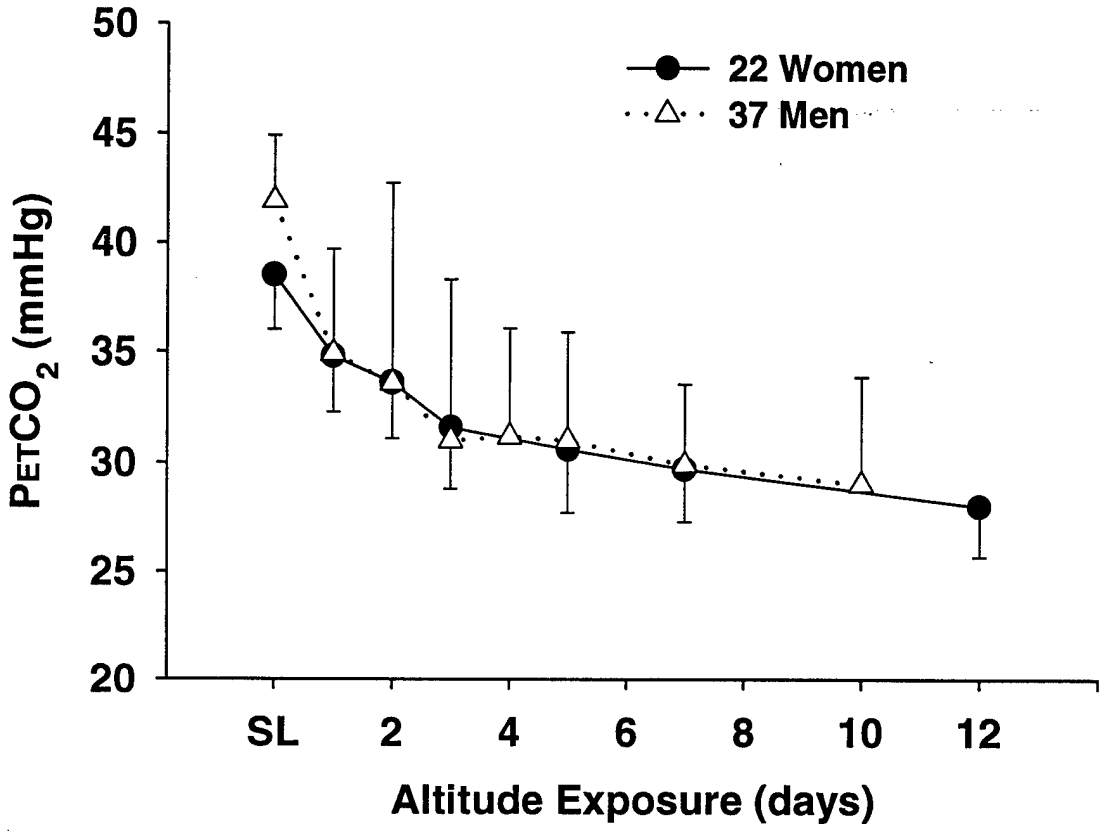

Fig. 6. Gender comparison of resting $P_{ET}CO_2$ measured at sea level and during 12 days sojourn at 4,300 m (Pikes Peak, CO). Womens' data from present study. Mens' data from (22). Men's error bars upwards, women's error bars downwards.

DISCUSSION

This study tested the hypothesis that women ascending to high altitude in their early luteal phase will have higher resting ventilations and accelerated ventilatory acclimatization compared to women in their follicular phase. Our results do not support this hypothesis. Due to low statistical power (β=0.39), we cannot conclusively rule out menstrual cycle effects on ventilatory acclimatization to high altitude. However, there were no meaningful differences between the follicular and luteal phase subjects in resting ventilation or ventilatory chemosensitivities during the first 3 days at high altitude. Nor were there any significant differences in the rate of ventilatory acclimatization during the first 3 days residence at 4,300 m.

There are several possible explanations for our findings. First, we have to consider the possibility that our subject sample did not accurately represent the population of young women with normal menstrual cycles and plasma levels of estradiol and progesterone. As in previous studies (9-12,17,18,24,26,28-30,32) of menstrual cycle phase affects on resting ventilation at sea level, resting ventilation was greater in our luteal group women compared to the follicular group. However, those studies used a repeated measures design in which the women subjects were tested in each cycle phase, thus eliminating a significant amount of the interindividual variability normally seen in ventilatory measures. Because we used a between-groups comparison, we may not have observed significant menstrual cycle effects on ventilation due to an inadequate sample size. We assumed that between groups, the observed difference in $P_{ET}CO_2$ would be about 66% of the difference observed within a subject (~2.7 mmHg) (11,12,24,28-30,32). Given an expected $P_{ET}CO_2$ difference of 1.8 mmHg, our prospective power analysis (α=0.05, β=0.8) recommended an n=23. We recruited and tested 27 subjects at sea level, but for various reasons did not obtain studies on 5 at high altitude. Nonetheless, our results do not even hint of a difference between the luteal and follicular phase groups at high altitude. Furthermore, attempts to minimize between subject variability by "normalizing" individual ventilatory data to a sea level reference value such as resting $P_{ET}CO_2$ did not reveal any significant differences between the rate or magnitude of the ventilatory acclimatization response in the follicular vs. luteal groups.

A second possible reason for not observing significant menstrual cycle effects on ventilation in our subject population may be the lack of adequate plasma progesterone levels to stimulate ventilation in the luteal phase of the cycle, or that our test schedule may not have coincided with several of the subjects when they were at their peak progesterone levels. To study ventilatory acclimatization in normally menstruating subjects obligates one to accepting significant fluctuations in ovarian hormone concentrations during the acclimatization period. Although attempts were made to test the subjects in their early to mid-luteal phase when progesterone concentrations were likely to be greatest, post-study analysis of plasma progesterone and estradiol samples revealed that our test days may have missed some of the subjects' peak progesterone levels. Furthermore, as a group, the women in the luteal phase did not have remarkably high plasma progesterone concentrations (Table 3), although they were within accepted clinical limits for normally menstruating women. Consequently, our luteal phase subjects may have experienced a lower level of progesterone stimulus to ventilation than expected. On the other hand, previous studies suggest a lack of correlation between plasma progesterone concentration and the corresponding rise in resting ventilation (4,19,20). Furthermore, our within subject repeated measures of ventilatory parameters at sea level revealed significant changes in resting ventilation consistent with previous reports, (9-12,17,18,24,26,28-30,32) suggesting that the level of progesterone observed in our subjects was adequate to stimulate ventilation.

A third possible reason for not observing any significant menstrual cycle phase effects on ventilation at high altitude is that the ovarian hormone effects are overwhelmed by the hypoxic stress of the environment. Compared to the ventilatory changes between the follicular and luteal phases reported at low altitudes, the hypoxia of 4,300 m produce much larger changes in ventilation. For example, many studies (11,12,24,28-30,32) report that $P_{ET}CO_2$ drops ~ 2.7 mmHg in the mid-luteal phase compared to the follicular phase. By comparison, within hours on Pikes Peak, $P_{ET}CO_2$ dropped by that amount, and by the third day, the drop in $P_{ET}CO_2$ was nearly three times the magnitude observed between the follicular and luteal phases at low altitudes. Other studies suggest that menstrual cycle phase effects on ventilation may be fragile. Most studies (8,9) of menstrual cycle effects on ventilation during exercise, for example, do not find significant differences between follicular and luteal phases, suggesting that stresses like exercise overwhelm any ovarian hormone modulation of

ventilation. Thus it is likely that at least during the initial phase of ventilatory acclimatization, menstrual cycle phase effects do not significantly influence the magnitude and time course of the acclimatization process.

Given that ovarian hormone concentrations are not stagnant within the follicular or luteal phases, we examined the ventilatory data to determine if resting ventilatory parameters at sea level or altitude were related to the endogenous progesterone or estradiol levels. We hypothesized that since progesterone is a ventilatory stimulant, resting ventilation would show a correlation with serum progesterone concentration. However, none of our measured ventilatory parameters demonstrated significant correlations with either serum concentration of ovarian steroid hormones (Fig. 2-3). As previously noted, most studies have not found correlations between the magnitude of change in resting ventilatory measures and serum progesterone or estradiol concentrations within the menstrual cycle or during preganancy (4,19,20,32). The lack of a significant correlation between ventilation and serum ovarian steroid hormone concentrations may reflect individual differences in ventilatory sensitivity to these hormones and/or the rather large interindividual variability in resting ventilation related to familial and possibly other factors such as aerobic fitness and behavioral influences on ventilation.

An important finding of the present study was that women demonstrated a wide range of interindividual differences in ventilation at sea level and high altitude, and the differences at altitude were related to ventilatory differences among individuals before ascent. Sea level normoxic resting $P_{ET}CO_2$ was related significantly to that at altitude on all days measured. These results in women are in agreement with those reported by Reeves et al. (22) in men at the same altitude and location. In fact, both the slopes and correlations of the relationships between the women's sea level resting $P_{ET}CO_2$ and their altitude values tend to be higher than reported in men (22), (Table 3). It is possible that menstrual cycle phase contributed to the large interindividual differences in resting resting $P_{ET}CO_2$ at sea level and altitude. The correlations reported in Table 4 were calculated using sea level resting $P_{ET}CO_2$ values obtained in the menstrual cycle phase corresponding to the phase the subject was in on ascent to altitude. In 11 women, we had at least one sea level resting $P_{ET}CO_2$ value in the menstrual cycle phase opposite to which they arrived at altitude. In these subjects, the correlations between preascent sea level resting $P_{ET}CO_2$ and their altitude values (days 1 and 2)

were lower when the sea level $P_{ET}CO_2$ used was measured in the opposite menstrual cycle phase to that at altitude (same phase r=0.71, opposite phase r=0.41, n=11). This observation suggests that the tightness of the relationship between sea level resting $P_{ET}CO_2$ and altitude ventilation is influenced by menstrual cycle phase.

Even if menstrual cycle phase did not alter ventilatory acclimatization to altitude, we expected the women to demonstrate a greater ventilatory response and possibly accelerated time course of ventilatory acclimatization than previously reported for men. Previous studies of women residing at high altitude had reported greater overall ventilation in women than men (6,13,16). Although we did not include men in our studies, we did use similar measurement methods and nearly identical ascent profiles to those used in earlier studies of men in the same laboratories the present studies were performed. Plotted in Fig. 6 are the resting $P_{ET}CO_2$ for 37 men at sea level and 4,300 m reported by Reeves et al. (22) and the resting $P_{ET}CO_2$ values for the 22 women in the present study. This figure is remarkable in that except for a lower resting $P_{ET}CO_2$ in women at sea level, the women's and men's values overlay each other at altitude. On the basis of this comparison, we conclude that women rapidly ascending to 4,300 m have similar levels of ventilation and follow a time course for ventilatory acclimatization identical to that previously reported for men under similar ascent conditions.

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